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EXAMINER	
PORTNER, VIRGINIA ALLEN	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/821,930	NERI ET AL.	
	Examiner	Art Unit	
	GINNY PORTNER	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/22/2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *1-18 and 35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-34* is/are rejected.

7)☒ Claim(s) *20-34* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-35 are pending.

Sequence Letter/Compliance

The instant Application is now in sequence compliance.

- The sequences locations shown on page 3, lines 16-18; page 19, lines 23, 26-28, 30-31;page 23, lines 2-4, 6-8, 11-13 and 31; page 24, lines 1, 3-4 and 7; Claims 7 and 10 and; Figures 1 and 6 and the table on page 34, Table 1 were amended to recite SEQ ID NOs.

Drawings

- The Brief Description of the Drawing has been amended to recite SEQ ID Nos that identify the amino acid sequences and nucleic acid sequences shown in Figures 1B and 6.

Oath/Declaration

1. The newly submitted Oath and Declaration correctly claims priority to two US Applications now pending in the United States Patent Office, and states that the Application claims foreign priority under 35 U.S.C. 120.

Specification

2. The disclosure is no longer objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01 The disclosure has been amended to remove the hyperlinks previously located at page 15, lines 5 and 7, hyperlinks to sites on the Internet are recited.

Election/Restriction

3. Applicant's election with traverse of Group IV, in the reply filed on February 23, 2007 is acknowledged. The traversal is on the ground(s) that all of the groups are related to each other and therefore would not be a serious burden. Applicant traversal that Group III should be combined with Group IV for examination.

The examiner upon reconsideration of the Election/Restriction set forth on October 23, 2006, has decided to rejoin groups III and IV as the methods are overlapping and can be examined together. Groups I, II and V will not be rejoined as Applicant's traversal with respect to these groups was not found persuasive for the reasons set forth below.

First, the classification system has no statutory recognition whether inventions are independent and distinct. For example, each class and subclass is comprised of numerous completely independent and distinct inventions.

Second, MPEP 803 states that restriction is proper between patentably distinct inventions where the inventions are (1) independent or distinct as claimed and (2) a serious search and examination burden is placed on the examiner if restriction is not required.

The term distinct is defined to mean that two or more subjects as disclosed are related, for example, as product and method of use, but are capable of separate manufacture, use or sale as

claimed, and are patentable over each other (see MPEP 802.1). In the instant situation, the inventions of Groups I, II, III-IV and V are drawn to distinct inventions which are related as separate products capable of separate functions. Restrictions between the inventions is deemed to be proper for the reason previously set forth.

In regard to burden of search and examination, MPEP 803 states that a burden can be shown if the examiner shows either separate classification, different field of search or separate status in the art. Trimethylstannylbenozoic acid is clearly a different product (Group V) that differs in structure, function and biological/chemical effect from the antibodies of Group I, II and III-IV. In the instant case a burden has been established in showing that the inventions of Groups I-V are classified separately necessitating different searches of issued US Patents. However, classification of subject matter is merely one indication of the burdensome nature of search. The literature search, particularly relevant in this art, is not co-extensive, because for example methods of detection would not be directed to methods of cancer therapy. Additionally, it is submitted that the inventions of Groups have acquired a separate status in the art. Clearly different searches and issues are involved in the examination of each Group.

For these reasons the restriction requirement is deemed to be proper and is therefore made Final.

4. Claims 1-18, 35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Groups I, II, V and , there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on February 23, 2007.

Claim Objections

5. Claims 20-34 are objected to because of the following informalities: Claims 20-34 depend directly or indirectly from a withdrawn claim and are therefore as stand alone claims are incomplete/unclear.

6. Claim 28 recites the phrase "the molecule capable of.... is represented by a photosensitizer and a radionuclide" and depends from claim 20 which recites the phrase "a molecule" (singular tense). Claim 28 appears to be setting forth a Markush group, and should recite the phrase ---selected from the group consisting of--- instead of the term [represented by]. Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 19 and 29-34 provides for the use of an antibody or conjugate (claim 19 "**is used**" claims 29-34 "**is** injected"), but, since the claim does not set forth any active voice methods steps. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced. How is the antibody of claim 19 used? Where, or in what or in whom is the antibody conjugate injected of claims 29-34?

Specification

10. The amendment filed February 23, 2007 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: See Table 1 comparison on next page. The changes made to Table 1, do not evidence original descriptive support in the instant Specification. Applicant is required to cancel the new matter in the reply to this Office Action. Amended

Table 1:

Sequences of selected anti-ED-B antibody clones

	VH chain			VL chain		
Clone	31-33*	50-54*	95-98*	32*	50*	91-96*
A2	SYA	AISGSG (SEQ ID NO. 27)	GLSI (SEQ ID NO. 28)	Y	G	NGWYPW (SEQ ID NO. 32)
G4	SYA	AISGSG (SEQ ID NO. 27)	SFSF (SEQ ID NO. 30)	Y	G	GGWLPY (SEQ ID NO. 33)
E1	SYA	AISGSG (SEQ ID NO. 27)	~~FPFY~~ FPFY (SEQ ID NO. 31)	Y	G	TGRIPP (SEQ ID NO. 34)
H10	SFS	SIRGSS (SEQ ID NO. 28)	~~FPFY~~ FPFY (SEQ ID NO. 31)	Y	G	TGRIPP (SEQ ID NO. 34)
L19	SFS	SIRGSS (SEQ ID NO. 28)	~~FPFY~~ FPFY (SEQ ID NO. 31)	Y	Y	TGRIPP (SEQ ID NO. 34)

Original

34

Table 1:

Sequences of selected anti-ED-B antibody clones

	VH chain			VL chain		
Clone	31-33*	50-54*	95-98*	32*	50*	91-96*
A2	SYA	AISGSG	GLSI	Y	G	NGWYPW
G4	SYA	AISGSG	SFSF	Y	G	GGWLPY
E1	SYA	AISGSG	FPFY	Y	G	TGRIPP
H10	SFS	SIRGSS	FPFY	Y	G	TGRIPP
L19	SFS	SIRGSS	FPFY	Y	Y	TGRIPP

Relevant amino acid positions (*: numbering according to Tomlinson et al. (1995) EMBO J., 14, 4628-4638) of antibody clones isolated from the designed synthetic libraries. Single amino acid codes are used according to standard IUPAC nomenclature.

Applicant has not pointed out where original descriptive support for the changes in the sequence for Table 1, can be found and is therefore considered New Matter.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

12. Claim 19 is rejected under 35 U.S.C. 102(b) as being anticipated by Sekiguchi et al (JP Kokai Patent Application No. Hei4 [1992]-169195, English translation, reference cited on Applicant's US PTO 1449]. Method, **Instant claim 19**: Sekiguchi et al disclose a method for using an improved affinity antibody, wherein the antibody is a monoclonal antibody (see claim 1) to the ED-B domain of fibronectin, the method comprising the step of "is used" (see page 11, paragraph 6 "By utilizing the antibody of this invention*, the cancer FN research method (see pages 21-22 and figure 1, starting

with paragraph (3)Antibody potency on page 21) and cancer diagnostic and treatment methods are provided".) Sekiguchi et al anticipates the instantly claimed invention as now claimed.

13. Claim 20, 25-26 are rejected under 35 U.S.C. 102(b) as being anticipated by Sekiguchi et al (JP Kokai Patent Application No. Hei4 [1992]-169195, English translation].

Composition, **Instant claims 20, 25-26**: Sekiguchi et al disclose antibody conjugates, wherein the conjugate comprises an improved affinity antibody, wherein the antibody is a monoclonal antibody (see claim 1) to the ED-B domain of fibronectin, conjugated to a radionuclide (see page 10, paragraph 4, "radioactive substances such as ^{125}I, ^{131}I, tritium etc", wherein the radioactive iodine emits gamma radiation and tritium is a beta emitter. Sekiguchi et al anticipates the instantly claimed invention as now claimed.

14. Claims 19, 20, 25, 29, 32 are rejected under 35 U.S.C. 102(a) as being anticipated by Neri et al (different inventive entity, WO97/45544).

Instant claim 19: Neri et al disclose the instantly claimed invention directed to a method for diagnosis (see page 22, lines 1-7 immunocytochemical staining of human and mouse tumour section with affinity matured anti-ED-B scFvs, as well as in vivo targeting and binding to human tumours and teratocarcinoma cells) and therapy of tumors associated with vascular proliferation, wherein the method uses an antibody with improved affinity (see page 20, lines 11-19 "scFvs CGS-1 and CGS-2"; page 22, Example 1 "Isolation of human scFvs specific to ED-B domain of human FN") for the ED-B domain of fibronectin, the method comprising the step of **"is used"** (see page 14, lines 7-12, "immunocytochemical staining" of human tumor tissue is diagnostic (in vitro diagnosis); see page 14, lines 28-36 "in vivo targeting agent which may be used to specifically demonstrate the presence and location of tumours expressing or associated with fibronectin ED-B"(in vivo diagnosis); see page 16, lines 19-26 "the present

invention also provides for the use of a specific binding member as above to use as a therapeutic reagent, for example when coupled, bound or engineered as a fusion protein to possess an effector function. A specific binding member according to the present invention may be used to target a toxin, radioactivity, T-cells, killer cells or other molecule to a tumour expressing or associated with the antigen of interest"). Neri et al anticipates the instantly claimed method of claim 19.

Instant claims 20, 25, 29, 32: Neri et al disclose the instantly claimed invention directed to a conjugate composition and a method of using the conjugate for diagnosis and/or treatment of angiogenesis related pathologies, wherein an antibody/molecule conjugate (see page 16, lines 6-7 radionucleotide … attached to an antibody"; page 16, lines 22-24 "coupled, bound or engineered… to target a toxin, radioactivity, T-cells, killer cells") is capable of inducing blood coagulation and blood vessel occlusion (see page 16, lines 15-26 "antibodies… in modified form, to deliver cytotoxic agents, or trigger coagulation within new blood vessels, thus starving the developing tumour of oxygen and nutrients and constituting an indirect form of tumour therapy") "**is injected**" (see Neri et al, page 17, line 23 "injection , e.g. intravenous" ; page 17, lines 33-34 "injection at the site of affliction") . Neri et al anticipates the instantly claimed compositions and methods as now claimed.

15. Claims 19, 20 and 29 are rejected under 35 U.S.C. 102(e) as being anticipated by Thorpe et al (US Pat. 6,093,339, filing date June 7, 1995).

16. Thorpe et al disclose the instantly claimed invention directed to conjugates that comprise:

a. an antibody with improved specificity (see monoclonal antibodies, col. 56, lines 38-43 and col. 57, claim 4), wherein the antibody binds to tumor associated fibronectin isoform, which includes the ED-B domain of fibronectin (see claims 17-18 and col. 8, lines 9-18; Table IV), and

b. a molecule capable of inducing blood coagulation and blood vessel occlusion (see claim 1, paragraph b; see col. 11, lines 65-68 and col. 12, lines 1-8; see col. 11, lines).

17. Thorpe et al describe monoclonal antibody (see '399, col. 4) conjugates (see '399, claim 93 "operatively linked", claim 84 "covalent bond or chemical cross-linker", all claims "coagulation factor" with binding region scFv (claim 4) specific to tumor-associated fibronectin isoforms (see'399 claims 17, 18). Among the coagulation factors disclosed are blood coagulation factors (see '399, col. 11), but also includes immunotoxins, immunoeffectors, and chemotherapeutic agents (see '399, col. 12, lines 40-43).

18. The antibody conjugates are for the purpose of administers the antibody conjugates specific to tumor associated fibronectin isoforms for the purpose of treating corneal graft neovascularization, diabetic retinopathy, (see '399, col. 9, lines 23-37), in vivo coagulation of tumor vasculature, causing tumor regression, and site-specific delivery of a coagulant using a bispecific antibody (see abstract; '399, col. 4, lines 57-67 human caner and tumor vasculature). The antibody conjugate is administered (see col. 65, lines 44-67) for treatment of disease (see col. 16 lines 59-67; see col. 9, lines 23-32), the disease including diabetic retinopathy, corneal graft neovascularization, vascular restenosis, treatment of benign or malignant tumors and inducing the coagulating process by specific exposure to coagulating agents.(see col. 6, lines 45-57) and is combinable with additional therapies to include radiotherapy, chemotherapy or immunotoxin antitumor therapy (see col. 14, lines 63-67 and col. 15, lines 1-3; col. 13, lines 27-36) and ophthalmic formulations (see col. 69, lines 65-67 and col. 70, lines 1-24).

19. Thorpe et al anticipates the instantly claimed invention as now claimed.

Claim Rejections - 35 USC § 103

20. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

21. Claims 21-24, 28, 30 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thorpe (US pat. 6,093,399) as applied to claims 19, 20 and 29, in view of Thorpe et al (May 1995).

See discussion of Thorpe et al '399 above. Thorpe et al show conjugates of antibodies specific to tumor associated fibronectin, ED-B, together with a molecule capable of blood vessel coagulation, and teach administration of the conjugate together with additional known tumor/vascular therapies, to include irradiation (radiotherapy) for the treatment of tumors and ocular conditions, but differs from the instantly claimed invention by failing to show the coagulation molecule to be a photosensitiser.

Thorpe et al (1995) teach the formulation of antibody conjugates that comprise a monoclonal antibody together with a photosensitizer, specifically tin chlorine e6 in an analogous art for the purpose of showing cell specific photoinduced cell lysis due to a point rupture resulting in cell injury, damage and death (see abstract, title, introduction).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the conjugate and method of Thrope et al '399, with the photosensitizer of Thorpe et al (1995) because both Thrope et al references are directed to antibody conjugates for targeted killing/lysis of cells, and Thorpe et al '399 teach that any molecule that is able to induced cell membrane damage resulting in blood vessel occlusion (coagulation) would serve in the formulation of a antibody conjugate and Thrope et al 1995 show

a photosensitizer (Tin (IV) choline e6) that is able to be conjugated to antibodies and when administered functions to accomplish the desired effect by using two orders of magnitude less conjugate(see page 2205, Thorpe et al 1995, col. 2, p. 1); the conjugate damages the cell membrane in a site specific manner upon activation with light (see Thorpe et al 1995, page 2205, col. 2, p. 3).

Absent a showing of unexpected results, the person of ordinary skill in the art would have been motivated by the reasonable expectation of success of substituting the molecule capable of coagulation of Thorpe et al '399, with the molecule capable of coagulation of Thorpe et al 1995 to obtain a conjugate that is able to induce blood vessel occlusion in a site specific manner because Thorpe et al 1995 teach photosensitizers are effective molecules for inducing membrane damage, and require two orders of magnitude less molecule/photosensitizer concentration to achieve the same or equivalent damaging effect and are readily conjugated to monoclonal antibodies for site specific delivery of the conjugate to the desired tumor cells (see abstract, such as melanoma cells) for induction of cell lysis, occlusion when conjugated to an anti-tumor associated fibronection (ED-B) antibody.

Thorpe et al '399 in view of Thorpe et al 1995 obviate the instantly claimed invention as now claimed.

22. Claims 20, 25-28, 29, 32, 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Neri and Zardi (April 1998) in view of US Patent Alvarez et al (US Pat. 4,741,900).

23. Neri et al describe antibodies specific to the ED-B domain of fibronectin (see Figure 1, page 44 "CGS-1 and CGS-2) and teach the delivery of toxic agents to a tumour for the occlusion

of the neovasculature, the antibodies being conjugated to drugs, radio-isotopes, toxin, photosensititisers for immunophotodynamic therapy (see section 2.2, page 48, col. 2, paragraph 3) but differs from the instantly claimed invention by failing to show the radionuclide to be bismuth-212 or bismuth-213.

24. Alvarez et al teach antibodies directed to oncofetal antigens (col. 3, line 28, section 2.1) conjugated (see claims) to an alpha emitter radionuclide, the radionuclide being either Bismuth 212 or Bismuth 213 (see col. 14, lines 57-59 (beta emitters), col. 14, lines 59-62 (alpha emitters) and claims15-16) in an analogous art for the purpose of producing radioimmunotherapy agents for killing tumor cells while causing minimal toxicity to non-targeted cells (see Brief summary text paragraph 69, section 2.4, col. 4) and administering the conjugate for in vivo therapy (see col. 14, section 5.5.1) by parenteral/intervenous administration (see col. 15, lines 2-4)

25. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the antibody conjugate of Neri et al that comprises a radioisotope with the alpha emitter radioisotope of Alvarez et al because Bismuth 212 and 213 are able to kill tumor cells while causing minimal toxicity to non-targeted cells.

26. In the absence of a showing of unexpected results, the person of ordinary skill in the art would have been motivated by the reasonable expectation of success of obtaining an anti-ED-B domain antibody-alpha emitter radionuclide Bismuth 212 or 213 radioimmunotherapy agent that could be injected into a subject to target, kill a tumor cell or induce coagulation because Neri et al teach anti-ED-B monoclonal antibodies with improved ED-B domain of fibronectin specificity for administration to cancer/tumor vascularized subjects and Alvarez et al successfully produced radioimmunotherapy agents that have high energy, are able to kill targeted cells with toxicity to

cells expressing the oncofetal antigen (Alverez et al, brief summary paragraph 61), and Neri et al teach improved antibodies specific to the oncofetal fibronectin ED-B antigen, and the Bismuth label of Alvarez et al when conjugated to an antibody results in minimal toxicity to non-targeted cells (see Alverez et al all claims and Brief summary paragraphs 61, 68 and 69). Neri et al in view of Alverez et al obviate the instantly claimed invention as now claimed.

27. Claims 20, 25-28, 29, 32, 33 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over (Neri and Zardi et al, different inventive entity) (April 1998) in view of Weller et al, US Patent 6,296,831 (effective filing date April 10, 1998).

28. Neri et al describe antibodies specific to the ED-B domain of fibronectin (see Figure 1, page 44 "CGS-1 and CGS-2) and teach the delivery of toxic agents to a tumour for the occlusion of the neovasculature, the antibodies being conjugated to drugs, radio-isotopes, toxin, photosensititisers for immunophotodynamic therapy (see section 2.2, page 48, col. 2, paragraph 3) but differs from the instantly claimed invention by failing to show the radionuclide to be bismuth-212 or bismuth-213.

29. Weller et al, US Patent 6,296,831 teach an alpha emitter radionuclides, the radionuclides being either Astatine-211, Bismuth 212 or Bismuth 213 (see claim 8) in an analogous art for the purpose of producing radioimmunotherapy agents for killing tumor cells while causing minimal toxicity to non-targeted cells (Brief Summary text "radiolabeled antibodies") and administering the conjugate for in vivo therapy .

30. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the antibody conjugate of Neri et al that comprises a radioisotope with the alpha emitter radioisotope of Weller et al because Astatine-211, Bismuth 212 and 213 are able to kill tumor cells while causing minimal toxicity to non-targeted cells.

31. In the absence of a showing of unexpected results, the person of ordinary skill in the art would have been motivated by the reasonable expectation of success of obtaining an anti-ED-B domain antibody-alpha emitter radionuclide Astatine-211, Bismuth 212 or 213 radioimmunotherapy agent that could be injected into a subject to target, kill a tumor cell or induce coagulation because Neri et al teach anti-ED-B monoclonal antibodies with improved ED-B domain of fibronectin specificity for administration to cancer/tumor vascularized subjects and Weller et al successfully produced radioimmunotherapy agents that have high energy, are able to kill targeted tumor cells (Weller et al, summary text paragraph 5), and Neri et al teach improved antibodies specific to the oncofetal fibronectin ED-B antigen and suggests radionuclide conjugation of the antibodies for radioimunotherapy, and the Astatine-211, or Bismuth 212 or 213 label of Weller when conjugated to an antibody results in minimal toxicity to non-targeted cells to provide for the desired radioimmunotherapy. Neri et al in view of Weller et al obviate the instantly claimed invention as now claimed.

32. Claims 20-24, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over (Neri and Zardi et al, different inventive entity, April 1998) in view of Rakestraw et al (PNAS, 1990). Neri et al describe antibodies specific to the ED-B domain of fibronectin (see Figure 1, page 44 "CGS-1 and CGS-2) and teach the delivery of toxic agents to a tumour for the

occlusion of the neovasculature, the antibodies being conjugated to photosensititisers for immunophotodynamic therapy (see section 2.2, page 48, col. 2, paragraph 3) but differs from the instantly claimed invention by failing to show the photosensitiser to be Tin (IV)chlorine e6.

33. Rakestraw et al teach monoclonal antibody-photosensitiser Tin (IV)chlorine e6 conjugates in an analogous art for the purpose of producing photodynamic agents for photolysis killing of targeted cells, the conjugates showing excellent retention of antigen binding activity relative to unmodified antibody.

34. It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the antibody conjugate of Neri et al that comprises a photosensititiser with the photosensitiser Tin (IV)chlorine e6 of Rakestraw et al because photosensitiser Tin (IV)chlorine e6 is able to induce photolysis/phototoxicity of cancer cells (melanoma) while causing minimal toxicity to non-targeted cells(see Rakestraw et al, page 4221, col. 1, paragraph 2, page 4220, Figure 3).

35. In the absence of a showing of unexpected results, the person of ordinary skill in the art would have been motivated by the reasonable expectation of success of obtaining an anti-ED-B domain antibody- photosensitiser Tin (IV)chlorine e6 photolysis/phototoxicity agent that could be injected into a subject to target and kill a tumor cell or induce coagulation because Neri et al teach anti-ED-B monoclonal antibodies with improved ED-B domain of fibronectin specificity for administration to cancer/tumor vascularized subjects and Rakestraw et al successfully produced photosensitiser Tin (IV)chlorine e6/antibody conjugate photolysis agents that have excellent retention of antigen binding activity and Neri et al teach improved antibodies specific to the oncofetal fibronectin ED-B antigen and suggests photosensitizer conjugation of the

antibodies for photosensitizer therapy, and the photosensitiser Tin (IV)chlorine e6 label of Rakestraw et al when conjugated to an antibody results in minimal toxicity to non-targeted cells to provide for the desired photolysis-immunotherapy. Neri et al in view of Rakestraw et al obviate the instantly claimed invention as now claimed.

Double Patenting

36. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

37. Claim 20 and 25 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 25 of U.S. Patent No. 7,273,924. Although the conflicting claims are not identical, they are not patentably distinct from each other because the allowed claim is directed to a genus of therapeutic agents that comprise an antibody to the ED-B domain of fibronectin that is defined to comprise radioactivity. The instantly claimed species is encompassed by the allowed genus of cancer therapy antibodies (allowed claim 25) that comprise radioactivity: "25. A pharmaceutical composition for cancer therapy or diagnostics comprising an

antibody or antibody fragment according to claim 1 in an effective amount for binding thereof to a fibronectin ED--B-containing cell, and a pharmaceutically-acceptable excipient." Genus defined in US 7,273,924: "The present invention also provides for the use of a specific binding member as above to use as a therapeutic reagent, for example when coupled, bound or engineered as a fusion protein to possess an effector function. A specific binding member according to the present invention may be used to target a toxin, **radioactivity**, T-cells, killer cells or other molecules to a tumor expressing or associated with the antigen of interest. "

38. Claims 20 and 25 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 44 and 45 of copending Application No. 10/321,558. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instantly claimed conjugate comprises a radionuclide that is capable of coagulation and occlusion and the copending claims 44-45 may comprise any radiolabelled or radioiodinated antibody that binds to the ED-B domain of fibronectin; the instantly claimed genus is anticipated by the copending species (radioiodinated conjugate).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

39. Any inquiry concerning this communication or earlier communications from the examiner should be directed to GINNY PORTNER whose telephone number is (571)272-0862. The examiner can normally be reached on flextime, but usually M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisors, Shanon Foley or Robert Mondesi, can be reached on 571-272-0898 or 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ginny Portner/
Examiner, Art Unit 1645
September 12, 2008

/Mark Navarro/
Primary Examiner, Art Unit 1645